REMARKS/ARGUMENTS

Claims 48 and 59-60 are pending in this application. Claims 55, 57, and 58 have been canceled. Claim 48 has been amended herein without prejudice and without acquiescence solely to more succinctly claim the same subject material. No new matter is entered herein.

Applicants regret the error regarding marking of claim 55 in the previous Response and thank the Examiner for examining the Response as filed.

The issues outstanding in this application are as follows:

Claim 48 is objected to for being wordy and unclear.

Claims 48, 55 and 57-60 as currently claimed allegedly do not have priority to provisional application 60/137,060.

Claims 55, 57 and 58 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to convey that the inventors had possession of the invention at the time of filing.

Claims 55, 57 and 58 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to enable any person skilled in the art to make and/or use the invention commensurate with the scope of these claims.

Claims 48, 55, 57 and 60 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Akazawa (J. Biol. Chem., 1995, 270:15, 8730-8738) in view of Schwarze (Science, 1999, Vol. 285, 1569-1572).

Claims 48, 55 and 57 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ben-Arie (Hum. Mol. Genet. 1996, Vol.5, 1207-1216) in view of Schwarze (Science, 1999, Vol. 285, 1569-1572).

Claims 48, 55 and 57 allegedly conflict with claim 12 (dependent on claim 9) of US Patent No. 6,838,444. This is an obviousness-type double patenting rejection.

I. Interview Summary

An interview with the undersigned, the Examiner, and a representative for the licensee in this case, Melissa Kolom, was conducted on June 28, 2004. The parties discussed the outstanding issues related to priority and the rejections under 35 U.S.C. §103(a) in this case. No agreement was reached.

II. Claim Objections

The Examiner objects to claim 48 for being wordy and unclear. Specifically, the Examiner objected to the phrase "an amino acid sequence that is not an atonal-associated amino acid sequence, wherein the amino acid sequence that is not atonal-associated amino acid sequence comprises a receptor binding domain of a bacterial toxin or a protein transduction domain." Claim 48 is amended herein to read more succinctly, yet encompasses the same claim breadth.

III. Issues of Priority

Claims 48 and 59-60 as currently claimed allegedly do not have priority to provisional application 60/137,060, filed June 1, 1999. Applicants respectfully disagree.

Claims 50 and 60 in provisional application 60/137,060 are as follows:

50. A composition comprising a *Math1* protein or gene in combination with a delivery vehicle, wherein the delivery vehicle causes a therapeutically effective amount of *Math1* to be delivered into a cell.

60 The composition of claim 50, wherein *Math1* and the receptor-binding domain of a bacterial toxin comprises a fusion protein.

On page 3 of the outstanding Action, the Examiner asserts the following:

> It is not readily apparent that the 'fusion protein' in claim 60 comprises Math1 because 'the receptor-binding domain of a bacterial toxin' in claim 60 lacks antecedent basis and because the bacterial toxin may act as a delivery vehicle using covalent bonds and not by protein expression from a hybrid gene comprising the bacterial toxin and Math1. As written, it cannot be determined that claim 60 encompasses a hybrid gene encoding a bacterial toxin and Math1.

First, regardless of whether or not these specific claims of the '060 provisional application are directed to a fusion between *Math1* and the receptor-binding domain of a bacterial toxin, the fact remains that there is still support for a fusion protein, both in claim 60 and in the '060 specification on page 8, lines 9-10, which states, "The composition for delivering *Math1* may even be a fusion protein." There is even support on page 32, lines 6-11 for fusions to facilitate expression or purification. Thus, there is no question that there is support for *Math1* delivered as a fusion protein in the '060 application.

The Examiner further alleges that there is no support for Hath1 in the '060 application. However, on page 33 of the '060 specification, it teaches that various modifications and combinations of the illustrative embodiments, as well as other embodiments of the invention, will be apparent to persons skilled in the art upon reference to the description. Given that there is support for the invention being described "in connection with the expression of homologs of the *Drosophila melanogaster* atonal gene..." (page 2, lines 2-3), Applicants assert that there is description for other atonal genes, including Hath1, particularly given that the Hath 1 sequence was known at the time of filing of the '060 provisional patent application priority document (see the GenBank submission provided in the Supplemental Information Disclosure Statement filed herewith). A skilled artisan would correlate the known Hath1 embodiment to the homologs noted in the specification of the '060 provisional patent application.

As stated above, the Examiner contends that there is no support for Math1 being in a fusion protein with a receptor-binding domain of a bacterial toxin in claim 60 of the '060 application. The Examiner alleges that it is not readily apparent that the fusion protein in claim 60 comprises a fusion protein because "the receptor-binding domain of a bacterial toxin in claim 60 lacks antecedent basis." The Examiner supposes that the bacterial toxin "may [*sic*] as a delivery vehicle using covalent bonds and not by protein expression from a hybrid gene comprising the bacterial toxin and Math1."

Regarding the embodiment of a receptor-binding domain of a bacterial toxin, it is not clear to Applicants how the claim can be interpreted in any other way than this domain being in a fusion protein. Claim 60 recites, "...**the receptor-binding domain of a bacterial toxin comprises a fusion protein**." Claim 60 does not recite that the receptor-binding domain serves as a delivery vehicle as alleged by the Examiner. Accordingly, it is abundantly apparent that

claim 60 encompasses a composition comprising a fusion protein comprising Math1 and a receptor-binding domain of a bacterial toxin.

Regarding the embodiment for Math1 as part of the fusion protein, Math1 must be part of the fusion protein of claim 60 because the claim is grammatically nonsensical if interpreted any other way. The term "Math1" is followed by the term "and," which indicates that the fusion protein comprises Math1 "***and***"...the receptor-binding domain of a bacterial toxin. In other words, the claim clearly states that a fusion protein ("C") comprises two parts of "A" and "B": Math 1 ("A") ***and*** a receptor binding domain ("B"). It is not clear to Applicants what the Examiner believes the term "Math1" refers to when the word "and" follows it, if not the receptor-binding domain. The claim clearly states that Math1 is in a fusion protein with the receptor-binding domain of a bacterial toxin.

In light of these comments, it is clear that pending claims 48 and its dependents, including both *Math1* and *Hath1* embodiments, have priority to the '060 provisional application. At the very least, the Math1 embodiments have the effective filing date of 6-1-99 in the '060 provisional application and the Hath1 embodiments have the effective filing date of 1-19-00 in the '993 provisional application.

IV. Issues under 35 U.S.C. § 112

A. Written Description

Claims 55, 57 and 58 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to convey that the inventors had possession of the invention at the time of filing. Solely in an effort to advance prosecution of the subject application, and not in acquiescence of the rejection, these claims are cancelled herein.

B. Enablement

Claims 55, 57 and 58 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to enable any person skilled in the art to make and/or use the invention commensurate with the scope of these claims. Solely in an effort to advance prosecution of the subject application, and not in acquiescence of the rejection, these claims are cancelled herein.

V. Issues under 35 U.S.C. § 103

A. Akazawa in view of Schwarze

Claims 48, 55, 57 and 60 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Akazawa (J. Biol. Chem., 1995, 270:15, 8730-8738; "Akazawa") in view of Schwarze (Science, 1999, Vol. 285, 1569-1572; "Schwarze"). These rejections are traversed for the reasons set forth below.

Akazawa teaches transfecting a MATH1 gene construct into a cell line for the purpose of transcriptional analysis. In other words, Akazawa introduces a nucleic acid molecule encoding Math1 into a cell line to determine if Math1 activates a reporter gene linked to a promoter of interest.

Schwarze teaches the delivery of fusion proteins produced *in vitro* into cells in an intact organism for the purpose of protein therapy, or treatment of disease. Therefore, even if a person of skill was searching for a way to enhance transfection of a MATH1 nucleic acid construct into a cell line, he would not have looked to Schwarze for inspiration.

It would not be obvious to a person of ordinary skill in the art, in the absence of an inventive mindset, to combine the teachings of the two references. First, there is no suggestion in Akazawa to use Math1 as a therapeutic agent in an intact organism. Second, the method of Schwarze would be inappropriate for the purposes of Akazawa. Akazawa transfected a vector encoding Math1 into a cell line in order to get stable, robust and continuous expression of Math1 to analyze activation of a reporter gene. Schwarze teaches delivering a protein fused to an HIV Tat protein into an intact organism, a process which by nature would not be stable or continuous. Therefore, the method of Schwarze is inappropriate for the purposes of Akazawa, and there would be no motivation to combine the two. Motivation is a factual question that cannot be resolved in "subjective belief and unknown authority." *In re Lee*, 277 F.3d 1338, 1344 (Fed. Cir. 2002), and Akazawa provides no reason or suggestion for enhancing the transfection of Math1, so there is no motivation to depart from the teachings of Akazawa to generate a Math1 fusion protein, much less to look to Schwarze and arrive at the presently claimed invention. In fact, the amount of transfection was certainly suitable enough for Math1 to "significantly activate" transcription of the promoter containing the E box element (page 8734, col. 2) and for "complete

inhibition" to occur upon co-expression with HES-1 (page 8735, col. 1). Akazawa provides no motivation to improve upon these successes.

In fact, during the aforementioned interview the Examiner admitted that nowhere in Akazawa was there teaching to improve the transfection efficiency but that one of skill in the art would always be motivated to improve transfection efficiency. Thus, the Examiner contends that the skilled artisan would be motivated to combine the teachings of Akazawa with Schwarze. First, the Examiner has no evidence that those of skill in the art would always seek to improve perfectly suitable transfection efficiency, and Applicants remind the Examiner that based on § MPEP 2144.03, and in keeping with *In re Zurko* (258 F.3d 1385, 59 USPQ2d 1697 (Fed. Cir. 2001)), an assessment of basic knowledge and common sense that is not based on any evidence in the record lacks substantial evidence support. The Examiner has provided no evidentiary support for the assertion that one of skill in the art would always be motivated to improve upon clearly sufficient transfection efficiency. The Examiner must provide specific factual findings predicated on sound technical and scientific reasoning to support his or her conclusion of common knowledge. *In re Chevenard*, 139 F.2d 713, 60 USPQ 241 (CCPA 1943). *In re Soli*, 317 F. 2d 941, 945-946, 137 USPQ 797, 800 (CCPA 1963). The Examiner needs to provide documentary evidence in the next Office Action if the rejection is to be maintained. See 37 CFR §1.104 (c)(2) and *Zurko*, 258 F.3d at 1386, 59 USPQ2d at 1697. If the Examiner is relying on personal knowledge to support the finding of what is known in the art, the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. See 37 CFR §1.104(d)(2).

Official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art, are capable of instant and unquestionable demonstration as being well-known. As noted by the court in *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970), the notice of facts beyond the record which may be taken by the examiner must be "capable of such instant and unquestionable demonstration as to defy dispute" (citing *In re Knapp Monarch Co.*, 296 F.2d 230, 132 USPQ 6 (CCPA 1961)) (emphasis added).

Furthermore, the notion that no motivation in the reference is required and that a skilled artisan would always seek to improve transfection efficiency is an improper *prima facie*

rejection, as stated in MPEP §2143, which notes that to establish a *prima facie* case of obviousness, there must be some suggestion or motivation in the reference or in the knowledge generally available to a skilled artisan to modify the reference. As even the Examiner acknowledges that there is no motivation in the Akazawa reference, the motivation in this case must come from the knowledge generally available to a skilled artisan to modify Math1 to become a fusion protein with a protein transduction domain. Applicants assert that the skilled artisan based on his general knowledge would recognize that the transfection efficiency was clearly suitable, and therefore there is no motivation from the source of the skilled artisan either. Again, if the Examiner maintains that one of skill in the art would find motivation from his general knowledge, then he needs to provide evidentiary support demonstrating so.

Applicants assert that the Examiner is employing impermissible hindsight to combine these references in alleging that Applicants' pending claims are obvious. A rejection based on hindsight is impermissible, particularly when it is based on the knowledge within the level of ordinary skill in the art at the time the claimed invention was made and when it does not include knowledge gleaned only from Applicants' disclosure. *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). Applicants assert that at the very least the Examiner is gleaning knowledge from Applicants' disclosure, considering that there is no motivation to improve transfection of Math1 in Akazawa.

Thus, Applicants respectfully request removal of this rejection.

B. Ben-Arie in view of Schwarze

Claims 48, 55 and 57 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ben-Arie (Hum. Mol. Genet. 1996, Vol.5, 1207-1216) in view of Schwarze (Science, 1999, Vol. 285, 1569-1572). Applicants respectfully disagree.

The Examiner states, "Ben-Arie taught transfecting eukaryotic cells with a vector encoding Hath 1." The Applicants are confused, as nowhere in this reference can be found discussion of transfecting eukaryotic cells with a Hath1 vector.

The Examiner points to pg. 1208, col. 1, lines 9-12, of Ben-Arie, which reads, "The human atonal homolog (*HATH1*) was cloned and mapped. It is highly similar to the mouse *Math1* gene (89% identity) and maps to human chromosome 4q22." The Examiner also points

out the sentence bridging cols. 1 and 2 and col. 2 lines 1 and 2, of Ben-Arie, stating, "To identify the human homolog of *Math1* a human genomic DNA library was screened with a *Math1* probe encompassing the ORF. Sequence analysis of the human homolog, *HATH1*, revealed that the coding region is intronless." The Examiner also states that "Sequencing requires transfection of prokaryotic cells to produce adequate amounts of *Hath1* DNA for sequence analysis."

To reiterate from the previous Response, the Applicants respectfully point out to the Examiner that screening a human genomic DNA library does not involve transfecting eukaryotic cells with any vector, much less a *HATH1* vector. Screening a genomic DNA library involves amplifying a bacteriophage λ or cosmid library in *E. coli* and then screening, for example, by colony lift and southern blot. There is no step that involves transfecting a plasmid into eukaryotic cells.

Furthermore, sequence analysis does involve producing adequate amounts of DNA to perform the sequencing reaction, but this is done in *E. coli* (a prokaryotic organism), not eukaryotic cells. Additionally, bacteria like *E. coli* are not transfected, they are transformed. Transfection in eukaryotic cells and transformation in prokaryotic cells are very different procedures. Ben-Arie transforms plasmid DNA into *E. coli* for the purpose of making more plasmid. Therefore, it would make no sense at all to combine the method of Schwarze, which involves putting a protein into eukaryotic cells, with the method of Ben-Arie, which involves putting a plasmid into prokaryotic cells. In fact, the Schwarze method would be completely inappropriate for the purposes of Ben-Arie as putting a protein into a cell does not result in the production of DNA. Thus, it would be completely illogical, and therefore not obvious, to combine the two methods.

The Examiner also points to pg. 1213, sentence bridging column 1 and 2 which reads, "Alu-PCR products of two YACs were used as probes for fluorescent *in situ* hybridization (FISH) on human metaphase spreads and hybridized to chromosome 4q22." The Examiner further points to the Materials and Methods section on page 1215, Physical Mapping of HATH1. The Examiner also states that "Chromosomal mapping requires the transfection of eukaryotic cells with the DNA for detection of the chromosome." The Applicants respectfully point out to the Examiner that FISH does not involve transfecting a vector into a cell. FISH involves fixing cells on a slide, including the steps of proteinase K or pepsin treatment, paraformaldehyde

fixation, DNA denaturation in formamide, and dehydration with ethanol. Fixed cells are then incubated (not transfected, in which a vector is introduced into live cells) with an *in vitro* transcribed and labeled, linear, single stranded probe (not a vector) that hybridizes to the gene of interest. This allows mapping of the gene of interest, usually in reference to one or more genes of known location. Clearly, there is no step that involves transfecting a vector into a eukaryotic cell. Therefore, the Examiner's argument that it would be obvious to combine the teachings of Ben-Arie with those of Schwarze is moot.

Furthermore, there is no suggestion to make any kind of fusion protein in Ben-Arie, much less one having an HIV Tat protein transduction domain, for example. Ben-Arie provides no reason or suggestion for enhancing the transfection of Hath1, so there is no motivation to depart from the teachings of Ben-Arie to generate a Hath1 fusion protein, much less to look to Schwarze and arrive at the presently claimed invention. Therefore, there is no motivation to employ Hath1 as a fusion protein with a protein transduction domain to enhance delivery. Similar to the discussion above for the Akazawa rejection, Applicants assert that there is no motivation provided either in the Ben-Arie reference or in the knowledge of the skilled artisan, particularly since the only instance of delivering a vector into a cell (for sequencing in *E. coli*) was plainly sufficient for its purpose. As such, one of skill in the art is not motivated to innovate the reagents of Applicants' invention by combining the Ben-Arie reference with Schwarze to employ a protein transduction domain.

Thus, Applicants respectfully request removal of this rejection.

VI. Double Patenting Issues

Claim 48 allegedly conflicts with claim 12 (dependent on claim 9) of US Patent No. 6,838,444. This is a double patenting rejection. Although the Applicants do not necessarily acquiesce to this rejection, a terminal disclaimer is filed herewith. Thus, Applicants respectfully request removal of this rejection.

VII. Conclusion

Applicants assert that in view of the above remarks each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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